Are European Standard Deviation Targets for Haemoglobin A_{1c} Too Strict?

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The Diabetes Control and Complications Trial (DCCT) has provided objective evidence for desirable glycaemic control in Type 1 patients and defines the benefits of good glycaemic control in terms of haemoglobin A_{1c} (HbA_{1c}) values. However, HbA_{1c} assays vary, leading to suggestions that glycaemic control be classified according to numbers of standard deviations (SD) from a local non-diabetic population mean. We have classified the glycaemic control of 339 UK Type 1 diabetic patients (182 male, 157 female, median age 36 (range 15–74) years) using the DCCT to set HbA_{1c} targets and compared this with the SD method. Using age matched controls (mean HbA_{1c} 4.02 %, SD 0.28 %, $n = 106$), SD guidelines classified 1 % of patients into good (HbA_{1c} <3SD from reference mean), 4 % into borderline (3–5SD) and 95 % into poor (>5SD) glycaemic control. When calibrating the same instrument to the DCCT analyser ($r = 0.996$), 37 % of patients had HbA_{1c} results lower than the 7 % median value found in the intensively treated DCCT group, while only 12 % of patients had values greater than the 9 % conventionally treated median HbA_{1c}. DCCT subjects with HbA_{1c} values of less than 8 % belonged predominantly to the intensively treated group. In this study, 71 % of patients fell into this category. Thus, guidelines based on numbers of SD away from a non-diabetic mean may overestimate the glycaemic control required to reduce microvascular complications in Type 1 patients. Standardizing to DCCT targets is more appropriate. © **1998 John Wiley & Sons, Ltd.**

***Diabet. Med.* 15: 920–923 (1998)**

KEY WORDS glycated haemoglobin; targets; complications

Received 6 August 1997; revised 30 June 1998; accepted 3 July 1998

Introduction

For most clinicians involved in the management of patients with diabetes, the measurement of glycated haemoglobin has become the cornerstone of treatment evaluation. This is because the measurement (usually in the form of haemoglobin A_{1c}) can give an objective indication of glycaemic control over the past 6–8 weeks.[1] However, the continued lack of standardization in the assay means that the same diabetic patient is likely to have different HbA_{1c} values depending on the method of analysis used. Consequently, this fundamental problem represents a major hurdle in defining target guidelines for the use by both patients and doctors.[2]

In an attempt to tackle this problem, and make analytical methods more comparable, it has been suggested that categories of glycaemic control be defined according to the number of standard deviations (SD) that a patient's HbA_1 or HbA_{1c} result lies from the non-diabetic mean value of the particular local assay. Indeed, the European Policy Group Guidelines of 1993[3] (which are only now being updated) suggested this as an alternative to using the Diabetes Control and Complications Trial (DCCT) HbA_{1c} method. Although the standard deviation 'cut-offs' used are necessarily arbitrary, the appeal of the guidelines' simplicity has lead to their wide adoption by diabetologists in the UK.

The rationale for wishing to achieve good glycaemic control stems from the results of the DCCT which showed conclusively that intensive treatment of Type 1 diabetic patients can delay the onset and progression of the long-term microvascular complications of retinopathy, nephropathy, and neuropathy.[4] What the study results also provided was the first objective evidence upon which the glycaemic control goals of Type 1 patients could be based.

With this in mind, this present study has assessed the glycaemic control of Type 1 patients attending a typical UK diabetic clinic by comparison with those participating in the DCCT, and compared this with the SD method described by the 1993 Policy Group for the treatment of Type 1 diabetes.

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 CCC 0742–3071/98/110920–04$17.50

Patients and Methods

Haemoglobin A_{1c} (HbA_{1c}) was measured on 339 consecutive Type 1 diabetic patients (182 male, 157 female, median age 36 (range 15–74) years) attending the Diabetes Unit, Gartnavel General Hospital, Glasgow, UK. A locally derived HbA_{1c} reference range was established using 106 non-diabetic staff from the same hospital (42 male, 64 female, fasting plasma glucose <6.4 mmol l^{-1}) who were age matched to the diabetic patients.

Haemoglobin A_{1c} was measured by ion exchange high performance liquid chromatography (HPLC) using a Biomen HA-8121 glycated haemoglobin analyser (Kyoto Daiichi Kagakiu Co. Ltd, Japan) which, according to the Wales External Quality Assessment Scheme (WEQAS), is currently the most popular glycated haemoglobin instrument in the UK.

The Biomen HbA_{1c} instrument was calibrated to a DCCT Primary Reference Laboratory HbA_{1c} analyser using 4 lyophilized samples supplied via WEQAS. Haemoglobin A_{1c} measurements equivalent to those from the DCCT analyser were calculated from the patient and non-diabetic values obtained using the Biomen instrument. The subjects in this study were then categorized according to European IDDM HbA_{1c} guidelines, which define good glycaemic control as an HbA_1 or HbA_{1c} value less than 3 standard deviations from an assay's mean non-diabetic value. Borderline control is between 3 and 5 standard deviations and poor control is above these limits.[3] In addition, the patients were also classified using recent American Diabetes Association (ADA) guidelines based on the findings of the DCCT.[5] These define the glycaemia goal for patients as a DCCT measured HbA_{1c} of <7 % and recommends action to be taken at a value of >8 %.

Poisson regression models have been derived from the results of the DCCT study to predict risks of retinopathy progression and hypoglycaemia at a given DCCT measured HbA_{1c} value.[6,7] These models were used to predict the number of episodes of each event in the present study's patients.

Results

Before calibration to the DCCT analyser, the mean HbA_{1c} value for the non-diabetic subjects using the Biomen instrument was 4.02 %, SD 0.28 %, giving a reference interval (mean ± 2SD) of 3.46–4.58 %. The median Biomen HbA_{1c} value amongst the diabetic patients was 7.1 (range 4.2–14.9) %.

The relationship between the Biomen HbA_{1c} instrument and the DCCT Primary Reference Laboratory was: Biomen $HbA_{1c} = 1.10 \times$ DCCT $HbA_{1c} - 0.91$, $r = 0.996$. Thus, the DCCT equivalent mean non-diabetic value was 4.48 %, SD 0.26 %, giving a reference interval of 3.97–4.99 %. The equivalent median DCCT HbA_{1c} was 7.3 %, range 4.6–14.4 % (Figure 1).

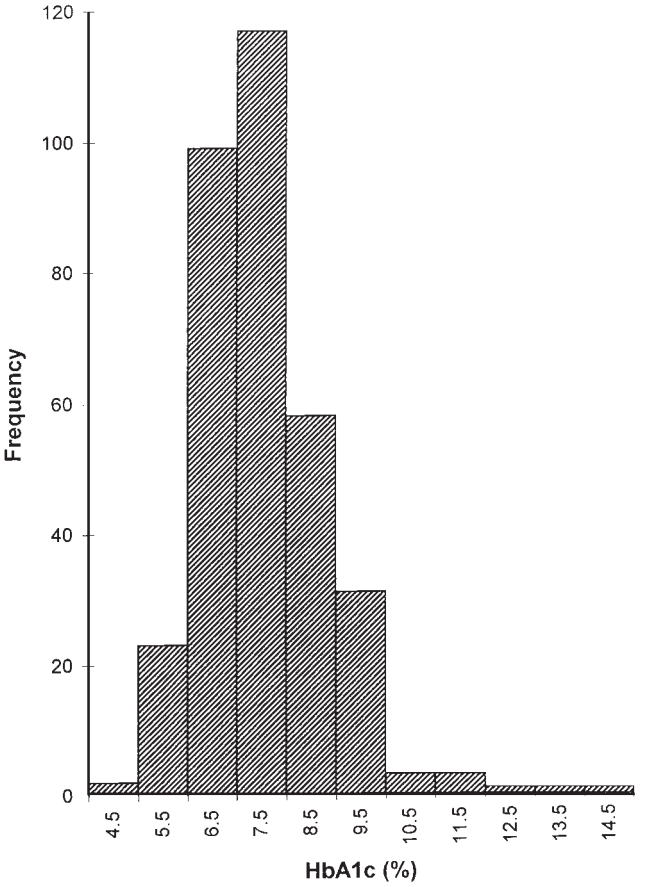

Figure 1. HbA_{1c} distribution in study subjects after calibration to DCCT

Using European criteria, only 3/339 patients (0.9 %) were in good glycaemic control (HbA_{1c} <3SD from reference mean value), with 14/339 (4.1 %) in borderline control (3–5 SD), and 322/339 (95 %) in poor glycaemic control (>5SD). Figure 2 gives the DCCT HbA_{1c} distribution of the study patients, and the percentage who had DCCT equivalent HbA_{1c} values <7 %, ≤ 8 % and >8 %.

From the DCCT Poisson distribution models it was estimated that during the following year there would be 8 episodes of retinopathy progression in the 339 patients. However, only 1 of these episodes would occur in the 126 patients with a DCCT HbA_{1c} of <7 %.

Discussion

The Diabetes Control and Complications Trial showed a 3-fold reduction in the onset or progression of diabetic retinopathy in a group of Type I diabetic patients who were intensively treated rather than conventionally treated.[4] In that trial, the median HbA_{1c} value was 7 % in the intensively treated group and 9 % in the conventionally treated group, with most patients below 8 % belonging to the intensively treated group (Figure 2). This study has shown that by having a median DCCT-equivalent HbA_{1c} of 7.3 %, the glycaemic control of a typical UK diabetic clinic is comparable to that obtained by intensive treatment during the DCCT.

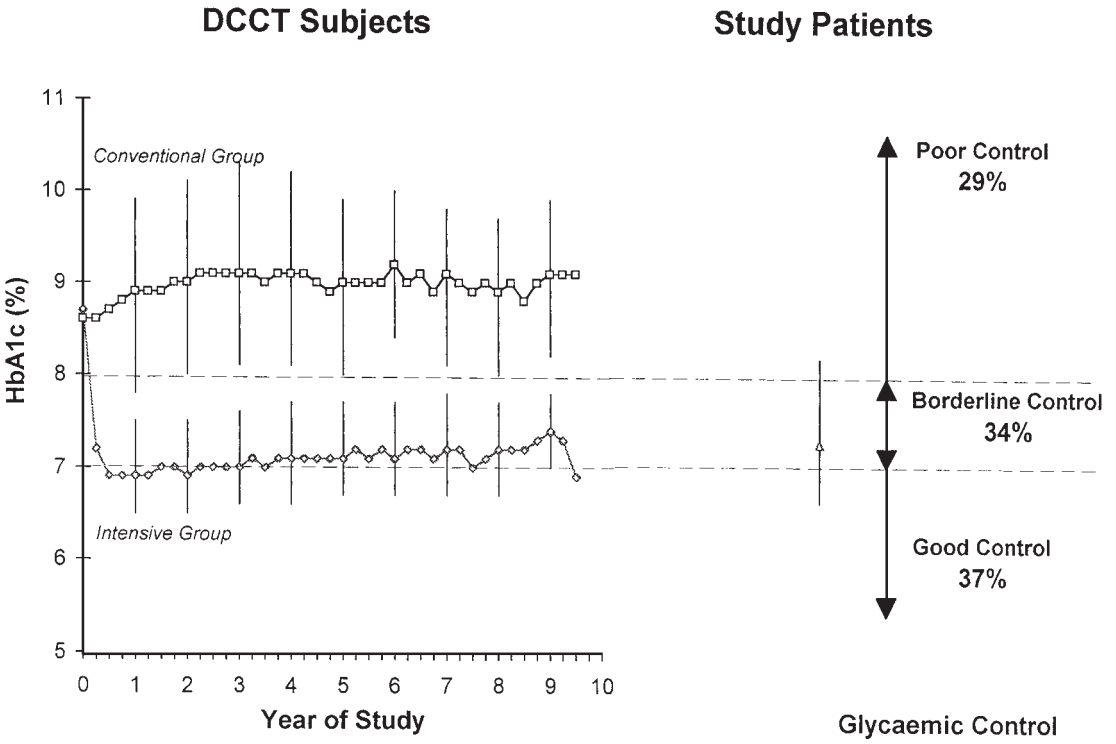

Figure 2. Median quarterly HbA_{1c} values, with the 25th and 75th percentiles of the yearly values in the intensively treated (◇) and conventionally treated (□) patients participating in the DCCT, together with DCCT-equivalent values of the present study's patients (△). Dashed lines at HbA_{1c} values of 7 % and 8 %. DCCT figure reproduced with permission of the *New England Journal of Medicine*

Because of the variability between HbA_{1c} assays, some authorities recommended the classification of glycaemic control according to the number of SD a patient's HbA_{1c} result lay from the local non-diabetic mean value. This definition was suggested as an alternative to using a DCCT-calibrated assay in the European Policy Group's Guidelines for the management of Type 1 diabetes in 1993,[3] and has been in common use since then. Our study clearly shows that, when using a HbA_{1c} analyser which is in routine use throughout the UK, such HbA_{1c} guidelines classify markedly more patients as poorly controlled in comparison to using the American Diabetes Association DCCT targets of 7 % and 8 %.[5] Indeed, the 1993 European IDDM guidelines would suggest that only 1 % of our patients are in good glycaemia while 95 % are in need of improved control at the same time as 37 % of the same patients achieve the DCCT HbA_{1c} goal of <7 % and 71 % attain a value ≤ 8 %. Thus, guidelines defining control according to SD ranges set much stricter targets for patients to achieve which, for many, may be unrealistic and unattainable.[8]

Much of the reason for the SD targets being so difficult to achieve is the 'tightness' of our non-diabetic reference range. Certainly, when calibrated to the DCCT instrument, our reference range for the Biomen instrument is both lower and much tighter (mean HbA_{1c} 4.48 %, SD 0.26 %) than that found by the DCCT group themselves (mean HbA_{1c} 5.05 %, SD 0.50 %). However, another study using the Biomen instrument has also found lower mean values than the DCCT when 200 subjects were analysed.[9] In fact, when reviewed critically, the DCCT group's reference range was derived using only 124 individuals, with HbA_{1c} values in some subjects as high as 6.62 %.[10] As regards the reference range SD, it is determined by both the biological and analytical variation of a glycated haemoglobin measurement. As methods improve (as they have done since the DCCT study was first conceived), so SDs become smaller, and reference ranges narrower. With particular reference to this study, analytical variation was further minimized by deriving the reference range over a period of only 3 days. Indeed the extremely small SD found here (0.26 % HbA_{1c}) is the same as the biological SD derived in a separate study using different subjects and another HPLC method.[11] Ironically, therefore, steady improvements in analytical methods and differences in deriving reference ranges have now lead to diabetic patients appearing more poorly controlled when using the European standard deviation cut-offs.

While this study has not attempted to establish the best glycaemic control targets for patients, a consideration of the additional benefits and risks by further reducing HbA_{1c} values from the DCCT value of 7 % to those of the SD targets is considered below.

Firstly, if the glycaemic control of our 339 diabetic patients remains stable, we can estimate from DCCT models[6] that there will be 8 episodes of retinopathy progression per year. However, only 1 of these episodes is likely to occur in the 126 patients whose DCCT-

equivalent HbA_{1c} is <7 %, while the remaining 7 episodes will occur in those patients who have HbA_{1c} values exceeding 7 %.

Secondly, the absolute reduction in retinopathy risk from having a DCCT measured HbA_{1c} value of 5.25 % (the SD method 'good control' cut-off) as opposed to 7 %, is the same as another patient falling from a HbA_{1c} of 10 % to 9.7 %.[6] Furthermore, the increased risk of severe hypoglycaemia by falling from 7 % to 5.25 % is 9-fold that of improving from 10 % to 9.7 %.[7] Moreover, with the exception of pregnant diabetic patients, in clinical practice it is often hugely difficult to achieve a fall in HbA_{1c} from 7 % to 5.25 %, whereas it is considerably less effort for both patients and carers to achieve the more modest fall from HbA_{1c} levels of around 10 %.

This is not to say that patients who can easily and safely achieve DCCT HbA_{1c} values of <7 % should be discouraged from doing so. However, it could be argued that, on a population basis, limited resources are best targeted at improving the glycaemia of poorly controlled patients since only a small reduction in HbA_{1c} will lead to substantial reductions in the absolute risk of microvascular complication progression at relatively little 'cost' of increasing hypoglycaemia.

When the 1993 European guidelines were formulated they were based on the best evidence available at that time. It could not have been envisaged that the ensuing improvements in analytical precision and the supplanting of HbA_1 measurement with HbA_{1c} would lead to the standard deviation targets becoming unachievable for most patients. With the continuing analysis of DCCT data and the reporting of the United Kingdom Prospective Diabetes Study (UKPDS), it is appropriate that the guidelines be updated according to their findings.

In conclusion, by using the DCCT as a yardstick, guidelines for diabetes control based on SD measurements from a non-diabetic mean overestimate the degree of glycaemic control required to substantially reduce the microvascular complications of Type 1 diabetes, and may thus be needlessly putting patients at an increased risk of hypoglycaemia. Targeting poorly controlled patients may be more beneficial than trying to ensure unfeasibly strict glycaemia for all patients.

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